CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

TUBERCULOSIS INFORMATION

- Treatment of Tuberculosis Disease in HIV-Infected Persons

The management of HIV-related TB disease is complex, and the clinical and public health consequences associated with the failure of treatment are serious. Whenever possible, the care for HIV-related TB should be provided by or in consultation with experts in management of both TB and HIV disease.

For each patient with newly diagnosed TB, a specific treatment and monitoring plan should be developed in collaboration with the local health department within 1 week of the presumptive diagnosis. This plan should include a description of the treatment regimen, the methods of assessing and ensuring adherence to the anti-TB regimen, and the methods of monitoring for adverse reactions.

Published guidelines recommend the use of antiretroviral therapy for patients infected with HIV. Widely used antiretroviral drugs available in the United States include the protease inhibitors (saquinavir, indinavir, ritonavir, efavirenz, and nelfinavir) and the nonnucleoside reverse transcriptase inhibitors (NNRTIs) (nevirapine and delavirdine). However, these inhibitors interact with rifamycin derivatives, such as rifampin and rifabutin, which are used to treat and prevent the mycobacterial infections commonly observed in HIV-infected patients. Because the most recent recommendations for the use of antiretroviral therapy strongly advise against interruptions of therapy, and because non–rifampin-containing alternatives for TB treatment are available, previous antituberculosis therapy options that involved stopping antiretroviral therapy to allow the use of rifampin are no longer recommended.

Regimen Options

The use of rifampin to treat TB is not recommended for patients who

- Will start treatment with an antiretroviral regimen that includes a protease inhibitor or an NNRTI at the same time they begin treatment for TB, **or**

- Have established HIV infection that is being maintained on such an antiretroviral regimen when TB is newly diagnosed and needs to be treated.

Two TB treatment options are currently recommended for these patients:

A rifabutin-based regimen

The initial phase of a **6-month** TB regimen for patients who are receiving therapy with protease inhibitors or NNRTIs consists of isoniazid, **rifabutin,** pyrazinamide, and ethambutol for the first 2 months (8 weeks). Once isoniazid and **rifabutin** susceptibility is documented, the initial phase should be followed by isoniazid and **rifabutin** to complete 6 months. Treatment should be prolonged to **9 months** for patients with delayed response to therapy.

An alternative nonrifamycin regimen that includes streptomycin

The initial phase of a **9-month** TB regimen for patients for whom the use of rifamycins is limited or contraindicated for any reason (e.g., intolerance to rifamycins, patient/clinician decision not to combine antiretroviral therapy with rifabutin) consists of a 2-month induction phase of isoniazid, ethambutol, pyrazinamide, and **streptomycin,** followed by isoniazid, pyrazinamide, and **streptomycin** administered 2-3 times per week for 7 months (30 weeks). Every effort should be made to continue the administration of **streptomycin** for the total duration of treatment. If streptomycin is not used for the recommended 9 months, **ethambutol** should be added to the continuation phase of the regimen and treatment duration should be prolonged from 9 months (38 weeks) to **12 months** (52 weeks).

Using a rifampin-based regimen continues to be recommended for the treatment of TB in HIV-infected patients

- Who have not started antiretroviral therapy, and both the patient and the clinician agree that it would be prudent to wait before starting such therapy, **or**

- For whom antiretroviral therapy with a protease inhibitor or NNRTI is not recommended

The following treatment option is recommended for these patients:
The initial phase of a **6-month** TB regimen for patients who are not candidates for antiretroviral therapy, or for those patients for whom a decision is made not to combine the initiation of antiretroviral therapy with TB therapy, consists of isoniazid, **rifampin,** pyrazinamide, and ethambutol (or streptomycin) for the first 2 months (8 weeks), followed by isoniazid and **rifampin** to complete 6 months. Isoniazid, **rifampin,** pyrazinamide, and ethambutol (or streptomycin) can be administered for the entire 6-month treatment period (36 weeks). Treatment should be prolonged to **9 months** for patients with delayed response to therapy.

Dosage Recommendations for the Treatment of TB in HIV-infected Children* and Adults

Drugs	Dose in mg/kg [Maximum Dose]					
	Daily		Twice-Weekly		Thrice-Weekly	
	Children*	Adults	Children*	Adults	Children*	Adults
Isoniazid	10-20 [300 mg]	5 [300 mg]	20-40 [900 mg]	15 [900 mg]	20-40 [900 mg]	15 [900 mg]
Rifampin	10-20 [600 mg]	10mg/kg [600 mg]	10-20 [600 mg]	10 [600 mg]	10-20 [600 mg]	10 [600 mg]
Pyrazinamide	15-30 [2 gm]	15-30 [2 gm]	50-70 [4 gm]	50-70 [4 gm]	50-70 [3 gm]	50-70 [3 gm]
Ethambutol**	15-25	15-25	50	50	25-30	25-30
Streptomycin	20-40 [1 gm]	15 [1 gm]	25-30 [1.5 gm]	25-30 [1.5 gm]	25-30 [1.5 gm]	25-30 [1.5 gm]
Rifabutin†	10-20 [300 mg] or *(150 mg)*§ or (*450 mg)*¶	5 [300 mg] or *(150 mg)*§ or (*450 mg)*¶	10 - 20 [300 mg] or 10 - 20 *(300 mg)* or (*450 mg)*¶	5 [300 mg] or 5§ (300 mg) or (*450 mg)*¶	Not Known Not Known Not Known	Not Known Not Known Not Known

* Children 12 years of age or younger

** Ethambutol (EMB) is not recommended for children who are too young to be monitored for changes in their vision. However, ethambutol should be considered for all children who have TB that is resistant to other drugs but susceptible to ethambutol. No maximum dosages for EMB but in obese patients dosage should be calculated on lean body weight.

† The concurrent use of Rifabutin (RFB) is contraindicated with ritonavir, saquinavir (Invirase™) and delavirdine. Information regarding the use of rifabutin with saquinavir (Fortovase™), amprenavir, efavirenz, and nevirapine is limited

§ If nelfinavir, indinavir, or amprenavir is administered with RFB, blood concentrations of the PIs decrease. Thus, when RFB is used concurrently with any of these drugs, the daily dose of RFB is reduced from 300 mg to 150 mg (the twice-weekly

dose of RFB is unchanged, however).

¶ If efavirenz is administered with RFB, blood concentrations of RFB decrease. Thus, when RFB is used with efavirenz, the dose of RFB for both daily and twice weekly administration should be increased from 300 mg to 450 mg.

No maximum dosages for EMB, but in obese patients dosage should be calculated on lean body weight.

Special Situations

Extrapulmonary TB. The basic principles that support the treatment of pulmonary TB in HIV-infected patients also apply to extrapulmonary forms of the disease. Most extrapulmonary forms of TB (including TB meningitis, tuberculous lymphadenitis, pericardial TB, pleural TB, and disseminated or miliary TB) are more common among persons with advanced-stage HIV disease than among patients with asymptomatic HIV infection. The drug regimens and treatment durations that are recommended for treating pulmonary TB in HIV-infected adults and children are also recommended for treating most patients with extrapulmonary disease. However, for certain forms of extrapulmonary disease, such as meningioma, bone TB, and joint TB, using a rifamycin-based regimen for at least 9 months is generally recommended.

Pregnant Women. HIV-infected pregnant women who have a positive *M. tuberculosis* culture or who are suspected of having TB disease should be treated without delay. Choices of TB treatment regimens for HIV-infected pregnant women are those that include a rifamycin. Although the routine use of pyrazinamide during pregnancy is not recommended in the United States because of inadequate teratogenicity data, the benefits of a TB treatment regimen that includes pyrazinamide for HIV-infected pregnant women outweigh the potential pyrazinamide-related risks to the fetus. Aminoglycosides (e.g, streptomycin, kanamycin, amikacin) and capreomycin are contraindicated for all pregnant women because of ototoxic effects on the fetus.

Children. In HIV-infected children, even in those who are too young to be evaluated for visual acuity and red-green perception, ethambutol at a dosage of 15 mg/kg body weight should generally be included as part of the initial regimen, unless the infecting source patient is known to have TB susceptible to isoniazid and rifampin. If drug susceptibility results are not available, a four-drug rifamycin-based regimen (e.g., isoniazid, rifamycin, pyrazinamide, and ethambutol) for 2 months, followed by intermittent administration of isoniazid and a rifamycin for 4 months, is recommended.

Drug-Resistant TB.

TB disease resistant to isoniazid only. The treatment regimen should generally consist of a rifamycin (rifampin or rifabutin), pyrazinamide, and ethambutol for the duration of treatment. Because the development of acquired rifamycin resistance would result in multidrug-resistent (MDR TB), clinicians should carefully supervise and manage TB treatment for these patients.

TB disease resistant to rifampin only. The 9-month treatment regimen should generally consist of an initial 2-month phase of isoniazid, streptomycin, pyrazinamide, and ethambutol. The second phase of treatment should consist of isoniazid, streptomycin, and pyrazinamide administered for 7 months. Because the development of acquired isoniazid resistance would result in MDR TB, clinicians should carefully supervise and manage TB treatment for these patients.

Multidrug-resistant TB (resistant to both isoniazid and rifampin). These patients should be managed by or in consultation with physicians experienced in the management of MDR TB. Most drug regimens currently used to treat MDR TB include an aminoglycoside (e.g., streptomycin, kanamycin, amikacin) or capreomycin, and a fluoroquinolone. The recommended duration of treatment for MDR TB in HIV-seropositive patients is 24 months after culture conversion, and posttreatment follow-up visits to monitor for TB relapse should be conducted every 4 months for 24 months. Because of the serious personal and public health concerns associated with MDR TB, health departments should always use directly observed therapy (DOT) for these patients and take whatever steps are needed to ensure adherence to the treatment regimen.

Adverse Reactions

Adverse reactions to TB drugs are relatively rare, but in some patients they may be severe. Clinicians who treat TB should be familiar with the methods of monitoring for adverse reactions and response to treatment. In some

situations (e.g., drug-resistant TB, pregnant patients, HIV-infected patients), expert consultation may be required. Before starting therapy, adults should have baseline laboratory tests, and adults and children who are taking ethambutol should have a baseline examination of their visual acuity.

During therapy, clinicians should monitor patients for side effects. They should instruct patients to look for the side effects commonly associated with the drugs they are taking. Also, clinicians should see patients at least once a month and ask them whether they are having side effects.

Patients who remain symptomatic or smear or culture positive after 2 months should be carefully reevaluated, and drug susceptibility tests for these patients should be repeated. Clinicians should consult a TB medical expert if the drug susceptibility results show resistance to any of the first-line drugs.

Case Management

One strategy that may be used to ensure that patients complete TB treatment is case management. There are three elements of case management: assignment of responsibility, systematic regular review, and plans to address barriers to adherence. In case management, a health department employee (case manager) is assigned primary responsibility and is held accountable for ensuring that each patient is educated about TB and its treatment, that therapy is continuous, and that contacts are examined. Some specific responsibilities may be assigned to other persons (e.g., clinic supervisors, outreach workers, health educators, and social workers).

A component of case management that helps to ensure that patients adhere to therapy is directly observed therapy (DOT). DOT means that a health care worker or another designated person watches the patient swallow each dose of TB medication. DOT ensures an accurate account of how much medication the patient really took. DOT should be considered for all patients because clinicians are often inaccurate in predicting which patients will adhere to medication on their own. However, it takes good case management in concert with DOT to really make DOT programs effective.

It is important that DOT be carried out at times and in locations that are as convenient as possible for the individual patient. Therapy may be directly observed in a medical office or clinic setting but can also be observed by an outreach worker in the field (i.e., the patient's home, place of employment, school, or other mutually agreed-upon place). In some situations, staff of correctional facilities or drug treatment programs, home health care workers, maternal and child health staff, or designated community members may provide DOT.

Monitoring Adherence

Pill counting and urine tests have been used to assess whether patients are adhering to therapy for TB. However, the only way to ensure that patients take every dose is to use directly observed therapy.

For More Information

For more information about implementing CDC guidelines, call your state health department.

To order the following publications, call the CDC's Voice and Fax Information System (recording) toll free at (888) 232-3228, then press options 2, 5, 1, 2, 2 (Note: You may select these options at any time without listening to the complete message). Request the publication number of the document you would like to order. You may also visit the Division of TB Elimination's Web site at www.cdc.gov/nchstp/tb.

Publication # 00-6453. American Thoracic Society. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med* 1994;149:1359-1374.

Publication # 99-5879. CDC. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. *MMWR* 1998;47(No. RR- 20).